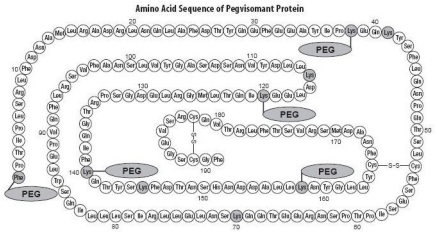
SOMAVERT - pegvisomant
Pharmacia and Upjohn Company

DESCRIPTION

SOMAVERT contains pegvisomant for injection, an analog of human growth hormone (GH) that has been structurally altered to act as a GH receptor antagonist.

Pegvisomant is a protein of recombinant DNA origin containing 191 amino acid residues to which several polyethylene glycol (PEG) polymers are covalently bound (predominantly 4 to 6 PEG/protein molecule). The molecular weight of the protein of pegvisomant is 21,998 Daltons. The molecular weight of the PEG portion of pegvisomant is approximately 5000 Daltons. The predominant molecular weights of pegvisomant are thus approximately 42,000, 47,000, and 52,000 Daltons. The schematic shows the amino acid sequence of the pegvisomant protein (PEG polymers are shown attached to the 5 most probable attachment sites). Pegvisomant is synthesized by a specific strain of *Escherichia coli* bacteria that has been genetically modified by the addition of a plasmid that carries a gene for GH receptor antagonist. Biological potency is determined using a cell proliferation bioassay.



Stippled residues indicate PEG attachment sites (Phe_1, Lys_{38}, Lys_{41}, Lys_{70}, Lys_{115}, Lys_{120}, Lys_{140}, Lys_{145}, Lys_{158})

SOMAVERT is supplied as a sterile, white lyophilized powder intended for subcutaneous injection after reconstitution with 1 mL of Sterile Water for Injection, USP. SOMAVERT is available in single-dose sterile vials containing 10, 15, or 20 mg of pegvisomant protein (approximately 10, 15, and 20 U activity, respectively). Vials containing 10, 15, and 20 mg of pegvisomant protein correspond to approximately 21, 32, and 43 mg pegvisomant, respectively. Each vial also contains 1.36 mg of glycine, 36.0 mg of mannitol, 1.04 mg of sodium phosphate dibasic anhydrous, and 0.36 mg of sodium phosphate monobasic monohydrate.

SOMAVERT is supplied in packages that include a plastic vial containing diluent. Sterile Water for Injection, USP, is a sterile, nonpyrogenic preparation of water for injection that contains no bacteriostat, antimicrobial agent, or added buffer, and is supplied in single-dose containers to be used as a diluent.

CLINICAL PHARMACOLOGY

Mechanism of Action

Pegvisomant selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with GH signal transduction. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGF binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS).

Pharmacokinetics

Absorption

Following subcutaneous administration, peak serum pegvisomant concentrations are not generally attained until 33 to 77 hours after administration. The mean extent of absorption of a 20-mg subcutaneous dose was 57%, relative to a 10-mg intravenous dose.

Distribution

The mean apparent volume of distribution of pegvisomant is 7 L (12% coefficient of variation), suggesting that pegvisomant does not distribute extensively into tissues. After a single subcutaneous administration, exposure (C_{max}, AUC) to pegvisomant increases disproportionately with increasing dose. Mean ± SEM serum pegvisomant concentrations after 12 weeks of therapy with daily doses of 10, 15, and 20 mg were 6600 ± 1330; 16,000 ± 2200; and 27,000 ± 3100 ng/mL, respectively.

Metabolism and Elimination

The pegvisomant molecule contains covalently bound polyethylene glycol polymers in order to reduce the clearance rate. Clearance of pegvisomant following multiple doses is lower than seen following a single dose. The mean total body systemic clearance of pegvisomant following multiple doses is estimated to range between 36 to 28 mL/h for subcutaneous doses ranging from 10 to 20 mg/day, respectively. Clearance of pegvisomant was found to increase with body weight. Pegvisomant is eliminated from serum with a mean half-life of approximately 6 days following either single or multiple doses. Less than 1% of administered drug is recovered in the urine over 96 hours. The elimination route of pegvisomant has not been studied in humans.

Drug-Drug Interactions
In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known (see **PRECAUTIONS, Drug Interactions**).

Special Populations

Renal
No pharmacokinetic studies have been conducted in patients with renal insufficiency.

Hepatic
No pharmacokinetic studies have been conducted in patients with hepatic insufficiency.

Geriatric
No pharmacokinetic studies have been conducted in elderly subjects.

Pediatric
No pharmacokinetic studies have been conducted in pediatric subjects.

Gender
No gender effect on the pharmacokinetics of pegvisomant was found in a population pharmacokinetic analysis.

Race
The effect of race on the pharmacokinetics of pegvisomant has not been studied.

CLINICAL STUDIES
One hundred twelve patients with acromegaly previously treated with surgery, radiation therapy, and/or medical therapies participated in a 12-week, randomized, double-blind, multi-center study comparing placebo and SOMAVERT. Following withdrawal from previous medical therapy, the 80 patients randomized to treatment with SOMAVERT received a subcutaneous (SC) loading dose, followed by 10, 15, or 20 mg/day SC. The three groups that received SOMAVERT showed dose-dependent reductions in serum levels of IGF-I, free IGF-I, IGFBP-3, and ALS compared with placebo at all post-baseline visits (Figure 1 and Table 1).

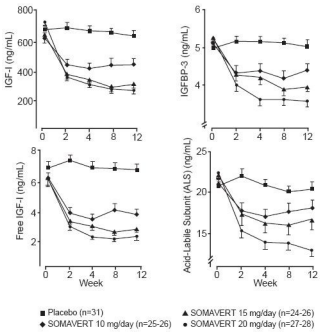


Figure 1. Effects of SOMAVERT on Serum Markers
(Mean ± Standard Error)
After 12 weeks of treatment, serum IGF-I levels were normalized in 10%, 39%, 75%, and 82% of subjects treated with placebo, 10, 15, or 20 mg/day of SOMAVERT, respectively (Figure 2).

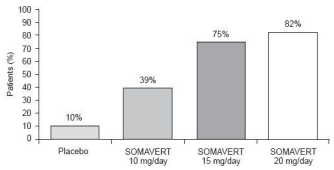


Figure 2. Percent of Patients Whose IGF-I Levels Normalized at Week 12
Table 2 shows the effect of treatment with SOMAVERT on ring size (standard jeweler's sizes converted to a numeric score ranging from 1 to 63), and on both the total and individual scores for signs and symptoms of acromegaly. Each individual score (for soft-tissue swelling, arthralgia, headache, perspiration and fatigue) was based on a nine-point ordinal rating scale (0 = absent and 8 = severe and incapacitating), and the total score was derived from the sum of the individual scores. Mean baseline scores were as follows: ring size = 47.1; total signs and symptoms = 15.2; soft tissue swelling = 2.5; arthralgia = 3.2; headache = 2.4; perspiration = 3.3; and fatigue = 3.7.

Table 1. Mean Percent Change from Baseline in IGF-I at Week 12 for Intent-to-Treat Population

	SOMAVERT			Placebo n=31
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
Mean percent change from baseline in IGF-I (SD)	-27 (28)	-48 (26)	-63 (21)	-4.0 (17)
SOMAVERT minus Placebo (95% CI for treatment difference)	-23* (-35, -11)	-44* (-56, -33)	-59* (-68, -49)	

*P<0.01

Table 2. Mean Change from Baseline (SD) at Week 12 for Ring Size and Signs and Symptoms of Acromegaly

	SOMAVERT			Placebo n=30
	10 mg/day n=26	15 mg/day n=24–25	20 mg/day n=26–27	
Ring size	-0.8 (1.6)	-1.9 (2.0)	-2.5 (3.3)	-0.1 (2.3)
Total score for signs and symptoms of acromegaly	-2.5 (4.3)	-4.4 (5.9)	-4.7 (4.7)	1.3 (6.0)
Soft-tissue swelling	-0.7 (1.6)	-1.2 (2.3)	-1.3 (1.3)	0.3 (2.3)
Arthralgia	-0.3 (1.8)	-0.5 (2.5)	-0.4 (2.1)	0.1 (1.8)
Headache	-0.4 (1.6)	-0.3 (1.4)	-0.3 (2.0)	0.1 (1.7)
Perspiration	-0.6 (1.6)	-1.1 (1.3)	-1.7 (1.6)	0.1 (1.7)
Fatigue	-0.5 (1.4)	-1.3 (1.7)	-1.0 (1.6)	0.7 (0.5)

Ring size at week 12 was smaller (improved) in the groups treated with 15 or 20 mg of SOMAVERT, compared with placebo. The mean total score for signs and symptoms at week 12 was lower (improved) in each of the groups treated with SOMAVERT, compared with the group treated with placebo.

Serum growth hormone (GH) concentrations, as measured by research assays using antibodies that do not cross-react with pegvisomant (see **PRECAUTIONS, Drug/Laboratory Test Interactions**), rise within two weeks of beginning treatment with SOMAVERT. The largest GH response was seen in patients treated with doses of SOMAVERT greater than 20 mg/day. This effect is presumably the result of diminished inhibition of GH secretion as IGF-I levels fall. As shown in Figure 3, when patients with acromegaly were given a loading dose of SOMAVERT followed by a fixed daily dose, this rise in GH was inversely proportional to the fall in IGF-I and generally stabilized by week 2. Serum GH concentrations also remained stable in patients treated with SOMAVERT for up to 18 months.

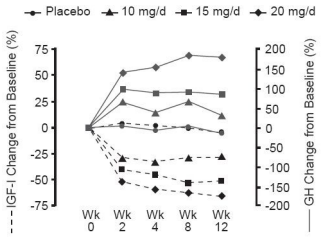


Figure 3. Percent Change in Serum GH and IGF-I Concentrations

Another cohort of 38 patients with acromegaly was treated with SOMAVERT in a long-term, open-label, dose-titration study and received at least 12 consecutive months of daily dosing with SOMAVERT (mean = 55 weeks). The mean (± standard deviation) IGF-I concentration at baseline in this cohort was 917 (± 356) ng/mL after withdrawal from previous medical therapy, falling to 268 (± 134) ng/mL at the end of treatment with SOMAVERT. Thirty-five of the 38 patients (92%) achieved a normal (age-adjusted) IGF-I concentration. After the first visit at which a normal IGF-I concentration was observed, IGF-I levels remained within the normal range at 92% of all subsequent visits over a mean duration of one year.

INDICATIONS AND USAGE

SOMAVERT is indicated for the treatment of acromegaly in patients who have had an inadequate response to surgery and/or radiation therapy and/or other medical therapies, or for whom these therapies are not appropriate. The goal of treatment is to normalize serum IGF-I levels.

CONTRAINDICATIONS
SOMAVERT is contraindicated in patients with a history of hypersensitivity to any of its components. The stopper on the vial of SOMAVERT contains latex.

PRECAUTIONS

General

Tumor Growth
Tumors that secrete growth hormone (GH) may expand and cause serious complications. Therefore, all patients with these tumors, including those who are receiving SOMAVERT, should be carefully monitored with periodic imaging scans of the sella turcica. During clinical studies of SOMAVERT, two patients manifested progressive tumor growth. Both patients had, at baseline, large globular tumors impinging on the optic chiasm, which had been relatively resistant to previous anti-acromegalic therapies. Overall, mean tumor size was unchanged during the course of treatment with SOMAVERT in the clinical studies.

Glucose Metabolism
GH opposes the effects of insulin on carbohydrate metabolism by decreasing insulin sensitivity; thus, glucose tolerance may increase in some patients treated with SOMAVERT. Although none of the acromegalic patients with diabetes mellitus who were treated with SOMAVERT during the clinical studies had clinically relevant hypoglycemia, these patients should be carefully monitored and doses of anti-diabetic drugs reduced as necessary.

GH Deficiency
A state of functional GH deficiency may result from administration of SOMAVERT, despite the presence of elevated serum GH levels. Therefore, during treatment with SOMAVERT, patients should be carefully observed for the clinical signs and symptoms of a GH-deficient state, and serum IGF-I concentrations should be monitored and maintained within the age-adjusted normal range (by adjustment of the dose of SOMAVERT).

Liver Tests (LTs)
Elevations of serum concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) greater than 10 times the upper limit of normal (ULN) were reported in two patients (0.8%) exposed to SOMAVERT during pre-marketing clinical studies. One patient was rechallenged with SOMAVERT, and the recurrence of elevated transaminase levels suggested a probable causal relationship between administration of the drug and the elevation in liver enzymes. A liver biopsy performed on the second patient was consistent with chronic hepatitis of unknown etiology. In both patients, the transaminase elevations normalized after discontinuation of the drug.
During the pre-marketing clinical studies, the incidence of elevations in ALT greater than 3 times but less than or equal to 10 times the ULN in patients treated with SOMAVERT and placebo were 1.2% and 2.1%, respectively.
Elevations in ALT and AST levels were not associated with increased levels of serum total bilirubin (TBIL) and alkaline phosphatase (ALP), with the exception of two patients with minimal associated increases in ALP levels (i.e., less than 3 times ULN). The transaminase elevations did not appear to be related to the dose of SOMAVERT administered, generally occurred within 4 to 12 weeks of initiation of therapy, and were not associated with any identifiable biochemical, phenotypic, or genetic predictors.
Baseline serum ALT, AST, TBIL, and ALP levels should be obtained prior to initiating therapy with SOMAVERT. Table 3 lists recommendations regarding initiation of treatment with SOMAVERT, based on the results of these liver tests (LTs).
Table 3. Initiation of Treatment with SOMAVERT Based on Results of Liver Tests

Baseline LT Levels	Recommendations
Normal	May treat with SOMAVERT. Monitor LTs at monthly intervals during the first 6 months of treatment, quarterly for the next 6 months, and then biannually for the next year.
Elevated, but less than or equal to 3 times ULN	May treat with SOMAVERT; however, monitor LTs monthly for at least one year after initiation of therapy and then biannually for the next year.
Greater than 3 times ULN	Do not treat with SOMAVERT until a comprehensive workup establishes the cause of the patient's liver dysfunction. Determine if cholelithiasis or choledocholithiasis is present, particularly in patients with a history of prior therapy with somatostatin analogs. Based on the workup, consider initiation of therapy with SOMAVERT. If the decision is to treat, LTs and clinical symptoms should be monitored very closely.

If a patient develops LT elevations, or any other signs or symptoms of liver dysfunction while receiving SOMAVERT, the following patient management is recommended (Table 4).

Table 4. Continuation of Treatment with SOMAVERT Based on Results of Liver Tests

LT Levels and Clinical Signs/Symptoms	Recommendations
Greater than or equal to 3 but less than 5 times ULN (without signs/symptoms of hepatitis or other liver injury, or increase in serum TBIL)	May continue therapy with SOMAVERT. However, monitor LTs weekly to determine if further increases occur (see below). In addition, perform a comprehensive hepatic workup to discern if an alternative cause of liver dysfunction is present.
At least 5 times ULN, or transaminase elevations at least 3 times ULN associated with any increase in serum TBIL (with or without signs/symptoms of hepatitis or other liver injury)	Discontinue SOMAVERT immediately. Perform a comprehensive hepatic workup, including serial LTs, to determine if and when serum levels return to normal. If LTs normalize (regardless of whether an alternative cause of the liver dysfunction is discovered), consider cautious reinitiation of therapy with SOMAVERT, with frequent LT monitoring.
Signs or symptoms suggestive of hepatitis or other liver injury (e.g., jaundice, bilirubinuria, fatigue, nausea, vomiting, right upper quadrant pain, ascites, unexplained edema, easy bruisability)	Immediately perform a comprehensive hepatic workup. If liver injury is confirmed, the drug should be discontinued.

Information for Patients

Patients and any other persons who may administer SOMAVERT should be carefully instructed by a health care professional on how to properly reconstitute and inject the product (see enclosed instructions).

Patients should be informed about the need for serial monitoring of LTs, and told to immediately discontinue therapy and contact their physician if they become jaundiced. In addition, patients should be made aware that serial IGF-I levels will need to be obtained to allow their physician to properly adjust the dose of SOMAVERT.

Laboratory Tests

Liver Tests

Recommendations for monitoring LTs are stated above (see **PRECAUTIONS, Liver Tests [LTs]**).

IGF-I Levels

Treatment with SOMAVERT should be evaluated by monitoring serum IGF-I concentrations four to six weeks after therapy is initiated or any dose adjustments are made and at least every six months after IGF-I levels have normalized. The goals of treatment should be to maintain a patient's serum IGF-I concentration within the age-adjusted normal range and to control the signs and symptoms of acromegaly.

GH Levels

Pegvisomant interferes with the measurement of serum GH concentrations by commercially available GH assays (see **Drug/ Laboratory Test Interactions**). Furthermore, even when accurately determined, GH levels usually increase during therapy with SOMAVERT. Therefore, treatment with SOMAVERT should not be adjusted based on serum GH concentrations.

Drug Interactions

Acromegalic patients with diabetes mellitus being treated with insulin and/or oral hypoglycemic agents may require dose reductions of these therapeutic agents after the initiation of therapy with SOMAVERT.

In clinical studies, patients on opioids often needed higher serum pegvisomant concentrations to achieve appropriate IGF-I suppression compared with patients not receiving opioids. The mechanism of this interaction is not known.

Drug/Laboratory Test Interactions

Pegvisomant has significant structural similarity to GH, which causes it to cross-react in commercially available GH assays. Because serum concentrations of pegvisomant at therapeutically effective doses are generally 100 to 1000 times higher than endogenous serum GH levels seen in patients with acromegaly, commercially available GH assays will overestimate true GH levels. Treatment with SOMAVERT should therefore not be monitored or adjusted based on serum GH concentrations reported from these assays. Instead, monitoring and dose adjustments should only be based on serum IGF-I levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Standard two-year rodent bioassays have not been performed with pegvisomant. Pegvisomant was not mutagenic in the Ames assay or clastogenic in the *in vitro* chromosomal aberration test in human lymphocytes. Pegvisomant was found to have no effect on fertility and reproductive performance of female rabbits at subcutaneous doses up to 10 mg/kg/day (10 times the maximum human therapeutic exposure based on body surface area, mg/m^2).

Pregnancy

Pregnancy Category B
Early embryonic development and teratology studies were conducted in pregnant rabbits with pegvisomant at subcutaneous doses of 1, 3, and 10 mg/kg/day. There was no evidence of teratogenic effects associated with pegvisomant treatment during organogenesis. At the 10-mg/kg/day dose (10 times the maximum human therapeutic dose based on body surface area), a reproducible, slight increase in post-implantation loss was observed in both studies. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, SOMAVERT should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether pegvisomant is excreted in human milk. Because many drugs are excreted in milk, caution should be exercised when SOMAVERT is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of SOMAVERT in pediatric patients have not been established.

Geriatric Use
Clinical studies of SOMAVERT did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

Laboratory Changes
Elevations of serum concentrations of ALT and AST greater than ten times the ULN were reported in two subjects (0.8%) exposed to SOMAVERT in pre-approval clinical studies (see **PRECAUTIONS, Liver Tests [LTs]**).

General
Nine acromegalic patients (9.6%) withdrew from pre-marketing clinical studies because of adverse events, including two patients with marked transaminase elevations (see **PRECAUTIONS, Liver Tests [LTs]**), one patient with lipohypertrophy at the injection sites, and one patient with substantial weight gain. The majority of reported adverse events were of mild to moderate intensity and limited duration. Most adverse events did not appear to be dose dependent. Table 5 shows the incidence of treatment-emergent adverse events that were reported in at least two patients treated with SOMAVERT and at frequencies greater than placebo during the 12-week, placebo-controlled study.
Table 5. Number of Patients (%) with Acromegaly Reporting Adverse Events in a 12-week Placebo-controlled Study with SOMAVERT*

Event	SOMAVERT			Placebo n=32
	10 mg/day n=26	15 mg/day n=26	20 mg/day n=28	
Body as a whole				
Infection†	6 (23%)	0	0	2 (6%)
Pain	2 (8%)	1 (4%)	4 (14%)	2 (6%)
Injection site reaction	2 (8%)	1 (4%)	3 (11%)	0
Accidental injury	2 (8%)	1 (4%)	0	1 (3%)
Back pain	2 (8%)	0	1 (4%)	1 (3%)
Flu syndrome	1 (4%)	3 (12%)	2 (7%)	0
Chest pain	1 (4%)	2 (8%)	0	0
Digestive				
Abnormal liver function tests	3 (12%)	1 (4%)	1 (4%)	1 (3%)
Diarrhea	1 (4%)	0	4 (14%)	1 (3%)
Nausea	0	2 (8%)	4 (14%)	1 (3%)
Nervous				
Dizziness	2 (8%)	1 (4%)	1 (4%)	2 (6%)
Paresthesia	0	0	2 (7%)	2 (6%)

Metabolic and nutritional disorders				
Peripheral edema	2 (8%)	0	1 (4%)	0
Cardiovascular				
Hypertension	0	2 (8%)	0	0
Respiratory				
Sinusitis	2 (8%)	0	1 (4%)	1 (3%)

*****Table includes only those events that were reported in at least 2 patients and at a higher incidence in patients treated with SOMAVERT than in patients treated with placebo.
†The 6 events coded as "infection" in the group treated with SOMAVERT 10 mg were reported as cold symptoms (3), upper respiratory infection (1), blister (1), and ear infection (1).The 2 events in the placebo group were reported as cold symptoms (1) and chest infection (1).

Immunogenicity
In pre-marketing clinical studies, approximately 17% of the patients developed low titer, non-neutralizing anti-GH antibodies. Although the presence of these antibodies did not appear to impact the efficacy of SOMAVERT, the long-term clinical significance of these antibodies is not known. No assay for anti-pegvisomant antibodies is commercially available for patients receiving SOMAVERT.

Post-Marketing Experience
Lipohypertrophy has been reported in <5% of patients following pegvisomant administration.
Asymptomatic, transient elevations in transaminases up to 15 times ULN have been observed in <2% of patients in the post-marketing experience. These reports were not associated with an increase in bilirubin, and there were no clinical consequences for these patients. Transaminase elevations normalized with time, most often after suspending treatment (SOMAVERT should be used in accordance with the information presented in Table 4 with respect to liver test abnormalities).

OVERDOSAGE
In one reported incident of acute overdose with SOMAVERT during pre-marketing clinical studies, a patient self-administered 80 mg/day for seven days. The patient experienced a slight increase in fatigue, had no other complaints, and demonstrated no significant clinical laboratory abnormalities.
In cases of overdose, administration of SOMAVERT should be discontinued and not resumed until IGF-I levels return to within or above the normal range.

Drug Abuse and Dependence
Available data do not demonstrate drug-abuse potential or psychological dependence with SOMAVERT. Radiolabeled pegvisomant does not cross the blood-brain barrier in rats.

DOSAGE AND ADMINISTRATION
A loading dose of 40 mg of SOMAVERT should be administered subcutaneously under physician supervision. The patient should then be instructed to begin daily subcutaneous injections of 10 mg of SOMAVERT. Serum IGF-I concentrations should be measured every four to six weeks, at which time the dosage of SOMAVERT should be adjusted in 5-mg increments if IGF-I levels are still elevated (or 5-mg decrements if IGF-I levels have decreased below the normal range).While the goals of therapy are to achieve (and then maintain) serum IGF-I concentrations within the age-adjusted normal range and to alleviate the signs and symptoms of acromegaly, titration of dosing should be based on IGF-I levels. It is unknown whether patients who remain symptomatic while achieving normalized IGF-I levels would benefit from increased dosing with SOMAVERT.
The maximum daily maintenance dose should not exceed 30 mg.
SOMAVERT is supplied as a lyophilized powder. Each vial of SOMAVERT should be reconstituted with 1 mL of the diluent provided in the package (Sterile Water for Injection, USP). Instructions regarding reconstitution and administration are included in the package of SOMAVERT and should be closely followed. To prepare the solution, withdraw 1 mL of Sterile Water for Injection, USP and inject it into the vial of SOMAVERT, aiming the stream of liquid against the glass wall. Hold the vial between the palms of both hands and gently roll it to dissolve the powder. **DO NOT SHAKE THE VIAL,** as this may cause denaturation of pegvisomant. Discard the diluent vial containing the remaining water for injection. After reconstitution, each vial of SOMAVERT contains 10, 15, or 20 mg of pegvisomant protein in one mL of solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear after reconstitution. If the solution is cloudy, do not inject it. Only one dose should be administered from each vial. SOMAVERT should be administered within six hours after reconstitution. Pegvisomant may be given in the thigh, buttocks, upper arm, or abdomen; the site of SC injections should be rotated daily to help prevent lipohypertrophy.

HOW SUPPLIED

SOMAVERT is available in single-dose, sterile glass vials in the following strengths:

10 mg (as protein) vial	NDC 0009-5176-01
15 mg (as protein) vial	NDC 0009-5178-01
20 mg (as protein) vial	NDC 0009-5180-01

Each package of SOMAVERT also includes a single-dose vial containing Sterile Water for Injection, USP.
The stopper on the vial of SOMAVERT contains latex.

Storage

Prior to reconstitution, SOMAVERT should be stored in a refrigerator at 2 to 8°C (36 to 46°F). Protect from freezing.
After reconstitution, SOMAVERT should be administered within six hours. Only one dose should be administered from each vial.

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SOMAVERT®
pegvisomant for injection

PATIENT INFORMATION

SOMAVERT (SOM-ah-vert) (pegvisomant for injection)

Read the patient information that comes with SOMAVERT before you start using it and each time you get a refill, because new information may have been added. The information in this leaflet does not take the place of talking to your doctor about your medical condition or your treatment. If there is anything you do not understand in the instructions, or cannot do, call the toll-free number listed at the end of this leaflet.

What is SOMAVERT?

SOMAVERT is a medicine used to treat patients who have acromegaly. Acromegaly is a disease caused by the body making too much growth hormone.

Who should not use SOMAVERT?

Do not use SOMAVERT if you are allergic to SOMAVERT or any of its ingredients. The active ingredient is pegvisomant, which includes polyethylene glycol. The inactive ingredients are glycine, mannitol, sodium phosphate dibasic anhydrous, and sodium phosphate monobasic monohydrate. **The stopper on the vial of SOMAVERT contains latex.**
SOMAVERT has not been studied in children.

Tell your doctor if you:

- are pregnant or plan to become pregnant. We do not know if SOMAVERT can harm your unborn baby. You and your doctor will have to decide if SOMAVERT is right for you.
- are breast-feeding. We do not know if SOMAVERT passes into your milk or if it can harm your baby.
- have diabetes.
- have or had liver problems.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.
Be sure to tell your doctor if you use:

- insulin or other medicines (oral hypoglycemic medicines) for diabetes. The doses of these medicines may need to be changed if you use SOMAVERT.
- narcotic painkillers (opioid medicines). Your dose of SOMAVERT may need to be changed if you use any of these medicines.

How should I use SOMAVERT?

- Read the detailed "Instructions for Use" at the end of this leaflet before using SOMAVERT.
- SOMAVERT is given once a day as an injection under the skin (subcutaneous).
- Your first dose, called a loading dose, will be given to you by your health care professional.
- Your health care professional will teach you or your caregiver how to inject SOMAVERT.

- If you forget to give yourself an injection of SOMAVERT, skip that dose. Get back on your schedule the next day. Do **not** inject a double dose to make up for a forgotten injection.

- If there is anything you do not understand in the instructions, or cannot do, call your health care professional or the toll-free number listed at the end of this leaflet.

What are the possible side effects of SOMAVERT?
Some patients who have used SOMAVERT have developed liver problems. Stop SOMAVERT right away and call your doctor if you get any of the following symptoms:
- your skin or the white part of your eyes turns yellow (jaundice).

- your urine turns dark.

- your bowel movements (stools) turn light in color.

- you do not feel like eating for several days.

- you feel sick to your stomach (nausea).

- you have unexplained tiredness.

- you have pain in the stomach area (abdomen).

Your doctor may do blood tests before and during your treatment with SOMAVERT to check that your liver is working correctly and to see how you are responding to SOMAVERT. Your dose of SOMAVERT may be changed based on these test results.
The most common side effects with SOMAVERT are pain, infection, reaction at the site of injection, flu symptoms, nausea, and diarrhea. These are not all of the possible side effects of SOMAVERT. For more information, ask your doctor or pharmacist.
INSTRUCTIONS FOR USE
Your health care professional shoud teach you how to mix and inject SOMAVERT.
SOMAVERT is packaged in dry powdered form. Before you use SOMAVERT, it must first be mixed with a liquid called a diluent. The diluent is in the same packaging with the medicine. It is called Sterile Water for Injection, USP. Use only this diluent for mixing SOMAVERT. Do not use any other liquid to mix the medicine.
Use only one dose from each vial (small bottle) of SOMAVERT.
Storage
Before you mix the powder and the liquid, store the package of SOMAVERT in a refrigerator (36 to 46°F). Do not freeze.
After mixing the powder and liquid, you may keep the mixed medicine at room temperature inside the vial or the syringe, but you must inject the mixed SOMAVERT within 6 hours. If you have not used the mixed medicine within 6 hours, throw it away.
Getting Started
Remove 1 package of SOMAVERT from the refrigerator. Let it warm up to room temperature for about 10 minutes while you get ready to prepare your injection.
1. Wash your hands with soap and warm water. Dry your hands well.

2. Gather the necessary supplies:
- The package of SOMAVERT that is now at room temperature, which contains 1 vial of powder (SOMAVERT) and 1 vial of liquid (diluent called Sterile Water for Injection, USP)
- One 1-cc syringe, with a 18- to 21-gauge, 1-inch or longer needle (this will be the "diluent syringe")
- One 1-cc insulin syringe, with a 27- to 30-gauge, 1/2-inch needle that is permanently attached to the syringe (this is the syringe you will use for the injection)
- Alcohol or antiseptic swabs
- Proper container for throwing away used needles.

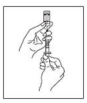
Mixing SOMAVERT

3. Remove the protective plastic caps from the tops of both vials (medicine and diluent). Do not touch the rubber vial stoppers. The stoppers are clean. If the stoppers are touched by anything, you must clean them with an antiseptic or alcohol swab before use. Carefully remove the cap from the syringe with the larger needle and set the cap aside. This is the diluent syringe.

4. Pull the plunger of the diluent syringe out to the 1-cc mark. With one hand, firmly hold the vial of diluent. With the other hand, push the needle of the diluent syringe straight through the center of the rubber stopper and deep into the vial. Gently push the plunger in until the air is injected into the vial.

5. Firmly hold the diluent vial and syringe together, with the needle still deeply inserted into the vial. Carefully turn the vial and syringe together upside down. Bring them to eye level.

6. Slide one hand carefully down the diluent vial so that with your thumb and forefinger you can firmly hold the neck of the vial, and with your other fingers you can hold the upper part of the syringe. With the other hand, slowly pull the syringe plunger out to slightly past the 1-cc mark.
   Check the syringe for air bubbles. If you see bubbles, tap the syringe barrel until the bubbles rise to the top of the syringe. Carefully push the plunger in to push only the air bubbles back into the vial. Recheck that 1 cc of diluent remains in the syringe. Then, pull the needle out of the vial. The vial should still have a lot of diluent in it. Do not use the leftover diluent.



7. Push the needle of the diluent syringe straight through the stopper of the vial of SOMAVERT (the one with the powder). Tilt the syringe to the side and gently push the plunger in to inject the diluent down the inner side of the vial of SOMAVERT. Be sure the diluent does not fall directly on the powder, but flows down the inside wall of the vial. When the syringe is empty, pull the needle out from the vial. Throw away the diluent vial with the leftover liquid in it, and the diluent syringe and needle as directed by your health care professional. To help prevent accidental injury, recap the needle only if taught to do so by your health care professional, and in the way you were told to do so by your health care professional.

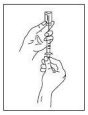
8. Hold the vial of SOMAVERT upright between your hands and gently roll it to dissolve the powder. **Do not shake the vial. Shaking may destroy the medicine.** The medicine mixture should be clear after the powder is dissolved. Do not inject the mixture if it looks cloudy or hazy, slightly colored, or if solid particles are visible. Tell your pharmacist and ask for a replacement vial. Do not throw the vial away because the pharmacist may ask that you return it. **Inject SOMAVERT within 6 hours of mixing it. If you wait more than 6 hours, you must throw away the mixture without injecting it.**

Preparing the Injection

9. Clean the rubber stopper of the vial of SOMAVERT with an antiseptic or alcohol swab. Carefully remove the cap from the insulin syringe (the one with the permanently attached needle) and set the cap aside. Pull the syringe plunger out to the 1-cc mark. With one hand, firmly hold the vial. With the other hand, push the needle straight through the center of the rubber stopper and deep into the vial. Gently push the plunger in until the air is injected into the vial.
   Firmly hold the vial and syringe together, with the needle still deeply inserted into the vial. Carefully turn the vial and syringe together upside down. Bring them to eye level.

10. As before, slide one hand carefully down the vial so that with your thumb and forefinger you can firmly hold the neck of the vial, and with your other fingers you can hold the upper part of the syringe. With the other hand, slowly pull the syringe plunger out to withdraw the full contents of the vial (1 cc). To keep the needle tip within the mixture, you may have to pull the needle out of the stopper slowly as you draw out the liquid.

Check the syringe for air bubbles. If you see bubbles, tap the syringe barrel until the bubbles rise to the top of the syringe. Carefully push the plunger in to push only the air bubbles back into the vial. Recheck that 1 cc of the mixture remains in the syringe. Then pull the needle out of the vial.
Recap the needle as directed by your health care professional to help prevent accidental injury while preparing the site for injection.



Giving the Injection
Subcutaneous (under the skin) injection sites may include the upper arm, upper thigh, abdomen (stomach area) and buttocks. Choose the injection site from one of the areas identified by your health care professional.
Choose a different injection site each day so lumps do not develop. Keep a record of each day's injection site as you take your daily dose of SOMAVERT. Do not use an area that has a rash or broken skin, or is bruised or lumpy.

11. Prepare the injection site area as taught by your health care professional. If you clean the site with an antiseptic or alcohol, let the skin dry before injecting the medicine. Uncap the needle if it was recapped.

12. With one hand, gently pinch up the skin at the site of injection. Hold the insulin syringe with the other hand. In a single, smooth motion, push the needle completely into the skin straight down, at a 90-degree angle.

13. Be sure to keep the needle all the way into the skin while you slowly push the syringe plunger in until the barrel is empty. Release the pinched skin and pull the needle straight out.

14. Do not rub the injection area. A small amount of bleeding may occur. If necessary, apply a clean, dry cotton pad over the area and press gently for 1 or 2 minutes, or until the bleeding has stopped.

15. Safely throw away needles and syringes as directed by your health care professional, according to local health regulations. Your health care professional or pharmacist can give you information about the right way to throw away the needles and syringes. Be sure to store and throw away your treatment materials in a way that lowers danger to others.

General information about the safe and effective use of SOMAVERT
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use SOMAVERT for a condition for which it was not prescribed. Do not give SOMAVERT to other people, even if they have the same symptoms you have.
Keep SOMAVERT and all medicines out of the reach of children.
This leaflet summarizes the most important information about SOMAVERT. If you would like more information, talk with your doctor or ask your doctor or pharmacist for the information about SOMAVERT that is written for health care professionals.
Questions about how to inject SOMAVERT?
Call Pharmacia & Upjohn Company toll-free at (800) 645-1280
For more information, please visit www.Somavert.com
Rx only

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